

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number: WO 99/64016 (43) International Publication Date: 16 December 1999 (16.12.99)
A61K 31/70, 38/21, 47/48 // (A61K 38/21, 31:70)		
(21) International Application Number:	PCT/EP99/03746	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date:	29 May 1999 (29.05.99)	
(30) Priority Data:	98110433.4 8 June 1998 (08.06.98) EP	
(71) Applicant:	F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basel (CH).	
(72) Inventor:	ZAHM, Friederike; Statzstrasse 18, D-79104 Freiburg (DE).	
(74) Agent:	LOESCHNER, Thomas; 124 Grenzacherstrasse, CH-4070 Basel (CH).	
(54) Title:	USE OF PEG-IFN-ALPHA AND RIBAVIRIN FOR THE TREATMENT OF CHRONIC HEPATITIS C	
(57) Abstract	<p>The present invention provides the use of PEG-IFN-α conjugates in association with Ribavirin for the manufacture of medicaments for the treatment of chronic hepatitis C infections. The present invention also provides a method for treating chronic hepatitis C infections in patients in need of such treating comprising administering an amount of PEG-IFN-α conjugate in association with an amount of Ribavirin effective to treat hepatitis C.</p>	
		<p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

Use of Peg-IFN-alpha and Ribavirin for the treatment of
chronic hepatitis C

The present invention relates to the field of treatment of chronic hepatitis C infections using an amount of a PEG-IFN- α conjugate in association with Ribavirin effective to treat hepatitis C.

- Interferons (IFNs) are naturally occurring proteins which have antiviral, 5 antiproliferative and immunoregulatory activity. Four distinct classes of interferons are known to exist in humans (Pestka et al. (1987) Ann. Rev. Biochem. 56, 727-777 and Emanual & Pestka (1993) J. Biol. Chem. 268, 12565-12569). The IFN α family represents the predominant class of IFNs produced by stimulated peripheral blood leukocytes (Pestka et al., loc. cit.); 10 Havell et al. (1975) Proc. Natl. Acad. Sci. USA 72, 2185-2187; Cavalieri et al. (1977) Proc. Natl. Acad. Sci. USA 74, 3287-3291), and lymphoblastoid and myeloblastoid cell lines (Familletti et al. (1981) Antimicrob. Agents. Chemother. 20, 5-9). The antiviral effect of IFN α is achieved not only by a direct influence on the viruses themselves, but by an activity on their target 15 cells in the sense of a protection against the virus infection. The interferons can exert effects on cancer tumors and can influence the immune system of the body on that, for example, they activate macrophages and NK cells and intensify the expression of various immunologically significant constituents of the cell membrane. Details of the preparation of interferon-cDNA and the 20 direct expression thereof, especially in *E. coli*, have been the subject of many publications. Thus, for example, the preparation of recombinant interferons is known, for example, from Nature 295 (1982), 503-508, Nature 284 (1980), 326-320, Nature 290 (1981), 20-26, Nucleic Acids Res. 8 (1980), 4057-4074, as well as from European Patents Nos. 32134, 43980 and 211148.

- 25 Combination therapy of IFN- α and Ribavirin in the treatment of chronic hepatitis C infections has been proposed (European Patent Application No. 707855), however, this treatment is not always effective.

The combination therapy of PEG-IFN- α conjugates and Ribavirin may thus be more effective than combination therapy of IFN- α and Ribavirin.

- 2 -

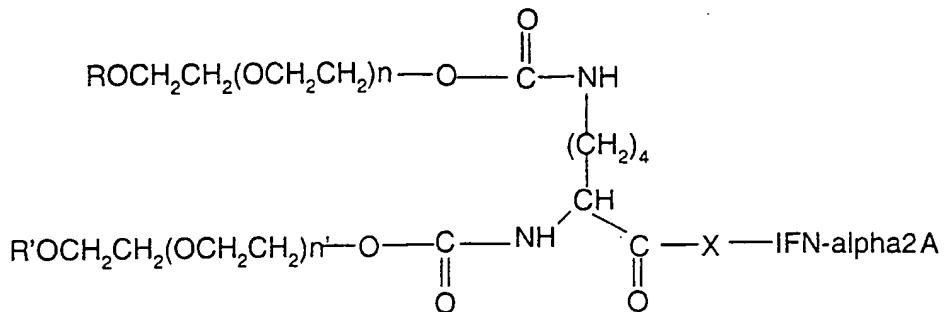
It has been observed that in the case of IFN- α , PEGylation increases circulating half-life and plasma residence time, reduces immunogenicity, decreases clearance and increases in vivo activity.

- The present invention provides therefore the use of PEG-IFN- α
- 5 conjugates in association with Ribavirin for the manufacture of medicaments for the treatment of chronic hepatitis C infections. In addition, the present invention provides a method for treating chronic hepatitis C infections in patients in need of such treating comprising administering an amount of PEG-IFN- α conjugate in association with an amount of Ribavirin effective to treat
- 10 chronic hepatitis C.

The term "PEG-IFN- α conjugate" as used herein includes IFN- α s derived from any natural material (e.g., leukocytes, fibroblasts, lymphocytes) or material derived therefrom (e.g. cell lines), or those prepared with recombinant DNA technology. Details of the cloning of IFN α and the direct expression thereof, especially in *E. coli*, have been the subject of many publications. The preparation of recombinant IFN α s is known, for example from Goeddel et al. (1980) *Nature* 284, 316-320 and (1981), *Nature* 290, 20-26, and European Patents Nos. 32134, 43980 and 211148. There are many types of IFN α such as IFN α I, IFN α 2; and further their subtypes including but not limited to IFN α 2A, IFN α 2B, IFN α 2C and IFN α II (also designated IFN α II or ω -IFN). The term "IFN α " also includes consensus IFN α available from Amgen or mixtures of natural and/or recombinant IFN α s. The use of IFN α 2A is preferred. The manufacture of IFN α 2A is described in European Patents Nos. 43980 and 211148.

- 25 The IFN- α is conjugated to a polymer such as a polyalkylene glycol (substituted or unsubstituted), for example, polyethylene glycol, to form PEG-IFN- α conjugate. Conjugation may be accomplished by means of various linkers known in the art, in particular by linkers such as those disclosed in European Patent Applications, Publication Nos. 0510356, 593868 and 809996.
- 30 The molecular weight of the polymer, which is preferably polyethylene glycol, may range from 300 to 70.000 daltons, and one or more, preferably one to three, polymers may be conjugated to the IFN- α . A preferred PEG-IFN- α conjugate has the formula:

- 3 -



where R and R' are methyl, X is NH, and n and n' are individually or both either 420 or 520.

Ribavirin, 1- β -D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation are described in U.S. Patent No. 4,211,771.

In accordance with this invention, PEG-IFN- α conjugate and Ribavirin are administered to the patient suffering from chronic hepatitis C infection in combined amounts effective to eliminate or at least alleviate one or more of the signs or symptoms of chronic hepatitis C including elevated ALT, positive test for anti-HCV antibodies, presence of HCV as demonstrated by a positive test for HCV-RNA, clinical stigmata of chronic liver disease and hepatocellular damage.

The dosage of PEG-IFN- α conjugate for practicing the combination therapy of this invention is about 33 to 540 microgram (mcg) per week, regardless of body weight, in one or two weekly administrations.

The dosage of Ribavirin for practicing this invention is about 400 to 1200 mg per day at least five days per week, preferably seven days per week. Based on the assumption of a patient weighing between 40 and 150 kg, the range of dosing is therefore between 10 and 30 mg per kg body weight per day. In a more specific embodiment the daily dosage of Ribavirin is 800-1200 mg. This daily dosage may be administered once per day in a single dose or in divided doses twice or thrice per day. Preferably the daily dosage of Ribavirin is administered in divided doses twice per day.

25 In accordance with this invention, the Ribavirin is administered to the patient in association with PEG-IFN- α conjugate, that is, the PEG-IFN- α conjugate dose is administered during the same or different periods of time that the patient receives doses of Ribavirin. In an embodiment of this

- 4 -

invention, at least one daily dose of Ribavirin is administered within the same week as at least one dose of PEG-IFN- α . In a more specific embodiment a majority of the Ribavirin administrations occur within the same week as one or more PEG-IFN- α administrations. In another specific embodiment, all or 5 substantially all of the Ribavirin administrations occur within the same week as one or more PEG-IFN- α administrations. At present PEG-IFN- α conjugate formulations are not effective when administered orally, so the preferred method of administering the PEG-IFN- α conjugate is parenterally, preferably by subcutaneous (sc) or intramuscular (im) injection. The Ribavirin may be 10 administered orally in capsule or tablet form in association with the parenteral administration of PEG-IFN- α conjugate. Of course other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, etc. Any form of administration will work so 15 long as the proper dosages are delivered without destroying the active ingredient.

The effectiveness of treatment may be determined by controlled clinical trials of the combination therapy versus monotherapy and / or combination therapy of IFN- α and Ribavirin. The efficacy of the combination therapy in 20 alleviating the signs and symptoms of chronic hepatitis C infection and the frequency and severity of the side effects will be compared with previous IFN- α monotherapy and / or combination therapy of IFN- α and Ribavirin. Three populations suffering from chronic hepatitis C infection are of relevance for evaluation. Either only one or all three patient populations will be studied 25 with the combination:

1. Patients previously untreated.
2. Patients previously treated with IFN- α and / or Ribavirin or any other drug and who had subsequently relapsed.
3. Patients who were non-responsive to previous treatment with IFN- α 30 and / or Ribavirin or any other drug.

The effectiveness of the combination therapy will be determined by the extent to which the previously described signs and symptoms of chronic hepatitis are alleviated.

- 5 -

Example

- A Phase III, Randomized, Multicenter, Efficacy and Safety Study Comparing the Combination of PEGylated-Interferon α2A and Ribavirin to REBETRON™ in the Treatment of Patients with Chronic HCV Infection
- 5 (CHC).

The primary purpose of this study is to compare the efficacy and safety of the combination of PEG-IFN-α2A and Ribavirin with REBETRON [Intron A + Rebetol (Schering /ICN brand of Ribavirin)] in the treatment of CHC. Equal numbers of patients (330 patients) are receiving either the combination of 10 PEG-IFN-α2A and Ribavirin or REBETRON for 48 weeks. A third group of patients (165 patients) is receiving PEG-IFN-α2A plus placebo for 48 weeks. The monotherapy arm provides a safety and efficacy comparator for the PEG-IFN-α2A combination arm.

15 The dose of Intron A is 3 Mio. in 0.5 ml solution, administered subcutaneous (sc) three times per week (tiw) for 48 weeks.

The dose of PEG-IFN-α2A is 180 µg, administered sc once per week, in combination with Ribavirin or placebo for 48 weeks.

20 The dose of Ribavirin and Rebetol is 1000 mg or 1200 mg based upon body weight, per day in split doses. Patients weighing < 75 kg (165 lbs) receive 1000 mg per day (400 mg in the morning and 600 mg in the evening), whereas patients weighing ≥ 75 kg receive 1200 mg per day (600 mg in the morning and 600 mg in the evening).

25 The primary efficacy parameters are the combined sustained virological [i.e., non-detectable HCV-RNA as measured by the AMPLICOR™ PCR assay (sensitivity ≥ 100 copies/ml)] and biochemical (normalization of serum ALT concentration) responses at the conclusion of the untreated follow-up period. To be considered a responder, patients must have a normal serum alanine aminotransferase (ALT) activity at both weeks 68 and 72 and no detectable virus at week 72.

30 Safety assessments are performed during screening, at baseline, at weeks 1, 2, 4, 6 and 8 and then every 4 weeks thereafter throughout the 48 week treatment period. Safety assessment continues during the subsequent 24-week follow-up period. Measures of safety include adverse events, vital signs, and

- 6 -

laboratory tests as well as tabulations of dose adjustments and premature withdrawals from treatment for safety or tolerability reasons.

Male and female patients aged 18 years or older with CHC who have not previously been treated with any form of IFN- α 2A or Ribavirin constitute the 5 patient population. Patients must have quantifiable HCV-RNA, persistently abnormal ALT and liver biopsy within 12 months consistent with CHC. Patients with other forms of liver disease, anemia, human immunodeficiency virus (HIV) infection, hepatocellular carcinoma, pre-existing severe depression or other psychiatric disease, cardiac disease, renal disease, seizure disorders, 10 or severe retinopathy are excluded.

A screening period (time from the first screening assessment to the first administration of test drug) of up to 35 days precedes treatment portion of the trial (48 weeks). Patients meeting all eligibility criteria are randomized to one of the three treatment regimens.

15 Patients in all groups who do not demonstrate a week 12 response [defined as either a decrease of at least one (1) log 10 unit in their HCV-RNA titer, as compared to baseline, or at least a 50% decrease (or normalization) of their serum ALT, as compared to baseline] are discontinued from therapy and considered non-responders. Patients meeting the week 12 definition of 20 response are discontinued from treatment at week 24 if they do not demonstrate either non-detectable HCV-RNA (<100 copies/ml) or normalization of ALT. Patients discontinued from treatment are followed thereafter only for safety. All patients meeting the weeks 12 and 24 response criteria are treated for 48 weeks. The primary efficacy parameter is the 25 combined virological and biochemical response (HCV-RNA <100 copies/mL and ALT normalization) at the end of the treatment-free follow-up period (24 weeks).

The currently known sustained virological response rates for the combination therapy of Intron A plus Rebetol and estimates of sustained 30 virological response rates for PEG-IFN- α 2A monotherapy for 48 weeks (based upon data obtained from the phase II study), and PEG-IFN- α 2A plus Ribavirin are summarized below:

- 7 -

Known and Estimated Virological Response Rates							
Treatment Group	Treatment Duration	Genotype 1 (A & B) EOT	Genotype 1 (A & B) EOF	Genotype non-1 EOT	Genotype non-1 EOF	Pooled EOT	Pooled EOF
N (Proportion of Total)		2/3		1/3		1/1	
Intron A	48 wks		9%		31%	29%	16%
Intron A plus Rebetol	48 wks		29%		65%	51%	41%
PEG-IFN	48 wks	60%	(29%) ^a	70%	(60%) ^a	62%	(40%) ^a
PEG-IFN plus Ribavirin	48 wks	(61%) ^a	(46%) ^a	70%	(70%) ^a	(66%) ^a	(53%) ^a

^a: Percent in parentheses are response rates estimated based on known response rates shown in the remainder of the table.

EOT: End-of-treatment virological response rate (clearance of virus).

5 EOF: End-of-follow-up virological response rate (clearance of virus).

- 8 -

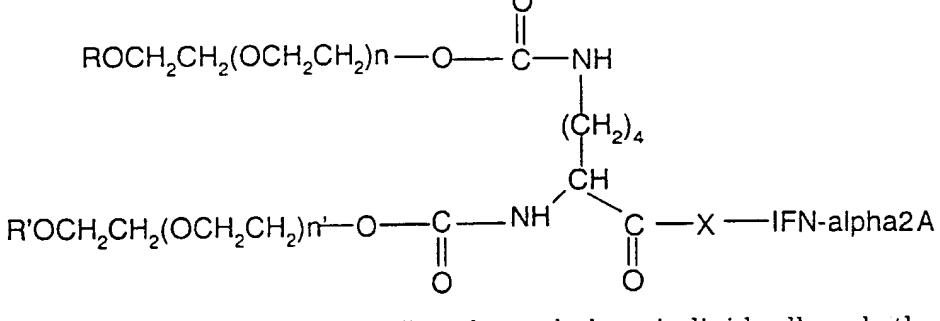
Claims

1. The use of PEG-IFN- α conjugates in association with Ribavirin for the manufacture of a medicament for the treatment of chronic hepatitis C infections.

5 2. Use according to claim 1 wherein the amount of the PEG-IFN- α conjugate is about 33 to 540 mcg per week.

10 3. Use according to claim 1 wherein the amount of Ribavirin is 400 to 1200 mg daily.

15 4. Use according to claims 1 to 3 wherein the PEG-IFN- α conjugate is
10 PEG-IFN- α 2A conjugate having the formula:



where R and R' are methyl, X is NH, and n and n' are individually or both either 420 or 520.

15 5. A method for treating chronic hepatitis C infections comprising
15 administering an amount of PEG-IFN- α conjugate in association with an amount of Ribavirin effective to treat chronic hepatitis C.

20 6. The method according to claim 5 wherein the amount of PEG-IFN- α conjugate administered in said method is about 33 to 540 mcg per week.

20 7. The method according to claim 5 wherein the amount of Ribavirin administered in said method is 400 to 1200 mg daily.

20 8. The method of any of claims 5 to 7 wherein the PEG-IFN- α conjugate administered is PEG-IFN- α 2A conjugate as defined above.

20 9. Use of a PEG-IFN- α conjugate and Ribavirin for the treatment of chronic hepatitis C infections.

- 9 -

10. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03746

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/70 A61K38/21 A61K47/48 // (A61K38/21, 31:70)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 707 855 A (SCHERING CORP) 24 April 1996 (1996-04-24) cited in the application claims ---	1-10
Y	WO 97 16204 A (SCHERING CORP) 9 May 1997 (1997-05-09) claims ---	1-10
Y	WO 95 13090 A (ENZON INC) 18 May 1995 (1995-05-18) page 17, line 35 -page 18, line 10 page 3, line 30 - line 33 ---	1-10
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 November 1999

29/11/1999

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Seegert, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03746

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 593 868 A (HOFFMANN LA ROCHE) 27 April 1994 (1994-04-27) cited in the application page 6, line 14 - line 29 page 10, line 6 - line 12; claims ----	1-10
Y	EP 0 510 356 A (HOFFMANN LA ROCHE) 28 October 1992 (1992-10-28) cited in the application page 15, line 47 - line 53 examples 8A,9,10,15,16,17,20,21,22,24 ----	1-10
P,Y	WO 98 48840 A (SCHERING CORP) 5 November 1998 (1998-11-05) claims -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03746

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
EP 0707855	A 24-04-1996	AU BR CA CN CZ HU JP NO PL SK WO	5919296 A 9608758 A 2221314 A 1190895 A 9703654 A 9802324 A 10506640 T 975309 A 323477 A 155997 A 9636351 A	A A A A A A T A A A A	29-11-1996 06-07-1999 21-11-1996 19-08-1998 15-07-1998 28-05-1999 30-06-1998 19-11-1997 30-03-1998 07-10-1998 21-11-1996
WO 9716204	A 09-05-1997	AU CA EP US	7473096 A 2236591 A 0858343 A 5908621 A	A A A A	22-05-1997 09-05-1997 19-08-1998 01-06-1999
WO 9513090	A 18-05-1995	AU AU EP HU JP NZ US US	691225 B 1179895 A 0730470 A 75533 A 9506087 T 276943 A 5711944 A 5951974 A	B A A A T A A A	14-05-1998 29-05-1995 11-09-1996 28-05-1997 17-06-1997 26-02-1998 27-01-1998 14-09-1999
EP 0593868	A 27-04-1994	US AT AU AU BG BR CA CN CN CN CZ DE DE ES FI HR HU JP JP LT LV LV MW MX NZ NZ OA PL SI SK ZA ZW	5382657 A 165102 T 668742 B 4478093 A 98067 A 9303469 A 2103829 A 1088936 A,B 1211578 A 1173500 A 9301693 A 69317979 D 69317979 T 2116376 T 933740 A 931094 A 67013 A 2859105 B 6192300 A 3174 B 10907 A 10907 B 7693 A 9305146 A 248452 A 264872 A 9850 A 300194 A 9300423 A 89893 A 9306098 A 11193 A	A T B A A A A A,B A A A D T T A A A B A A A A A A A A A A A A A A	17-01-1995 15-05-1998 16-05-1996 03-03-1994 15-11-1994 22-03-1994 27-02-1994 06-07-1994 24-03-1999 18-02-1998 13-04-1994 20-05-1998 20-08-1998 16-07-1998 27-02-1994 30-06-1997 30-01-1995 17-02-1999 12-07-1994 27-02-1995 20-12-1995 20-04-1996 08-06-1994 31-03-1994 21-12-1995 26-01-1996 15-08-1994 05-04-1994 31-03-1994 06-04-1994 01-03-1994 23-03-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03746

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0510356	A 28-10-1992	US 5595732 A		21-01-1997
		AT 176159 T		15-02-1999
		AU 657311 B		09-03-1995
		AU 1316092 A		01-10-1992
		AU 671045 B		08-08-1996
		AU 7761594 A		12-01-1995
		BG 60800 B		29-03-1996
		CA 2063886 A		26-09-1992
		CN 1065465 A, B		21-10-1992
		CN 1175465 A		11-03-1998
		CS 9200871 A		14-10-1992
		DE 69228269 D		11-03-1999
		DE 69228269 T		08-07-1999
		ES 2128329 T		16-05-1999
		FI 921267 A		26-09-1992
		GR 3030049 T		30-07-1999
		HU 9500259 A		28-09-1995
		JP 2637010 B		06-08-1997
		JP 5117300 A		14-05-1993
		MW 1892 A		12-01-1994
		MX 9201298 A		01-10-1992
		NZ 242084 A		23-12-1993
		NZ 248022 A		23-12-1993
		OA 9760 A		30-11-1993
		RO 109543 A		30-03-1995
		SI 9210294 A		31-10-1995
		US 5849860 A		15-12-1998
		US 5539063 A		23-07-1996
		US 5792834 A		11-08-1998
		US 5559213 A		24-09-1996
		US 5747646 A		05-05-1998
		US 5834594 A		10-11-1997
		ZW 4392 A		23-09-1992
WO 9848840	A 05-11-1998	US 5908621 A		01-06-1999
		AU 7249098 A		24-11-1998